Cell Cycle and Chemotherapy

Introduction

This is a true pharmacology lesson. The goal is to offer memory techniques to associate the names of drugs with their location in the cell cycle (including cell-cycle agnostic), provide an advanced organizer for the most commonly tested side effects, and talk about new stuff like targeted therapies and growth colony stimulating drugs. There is **NO** need, at this level, to link a diagnosis to a treatment regimen. Chemotherapeutic regimens are prescribed by oncologists, so should be known only to oncologists. Test-takers should never be asked to take a cancer diagnosis by name and produce the four or five agents to treat that cancer. Focus instead on knowing the individual drugs we teach you, major side effects, where they work within the cell cycle, and some generalities of chemotherapy side effects.

The Nadir and Generalized Side Effects

We'll discuss log-kill hypothesis specifically in #10 *General Concepts in Neoplasia*. The idea is that there are a lot of cancer cells. A lot. And we give chemo to kill them. We give multiple drugs at once so that no matter where they are in the cell cycle, we get those cells. And we're really good at it, too. But we can never get them all. The problem with this strategy is that by being really good at killing cancer cells, we're also really good at **killing healthy cells**.

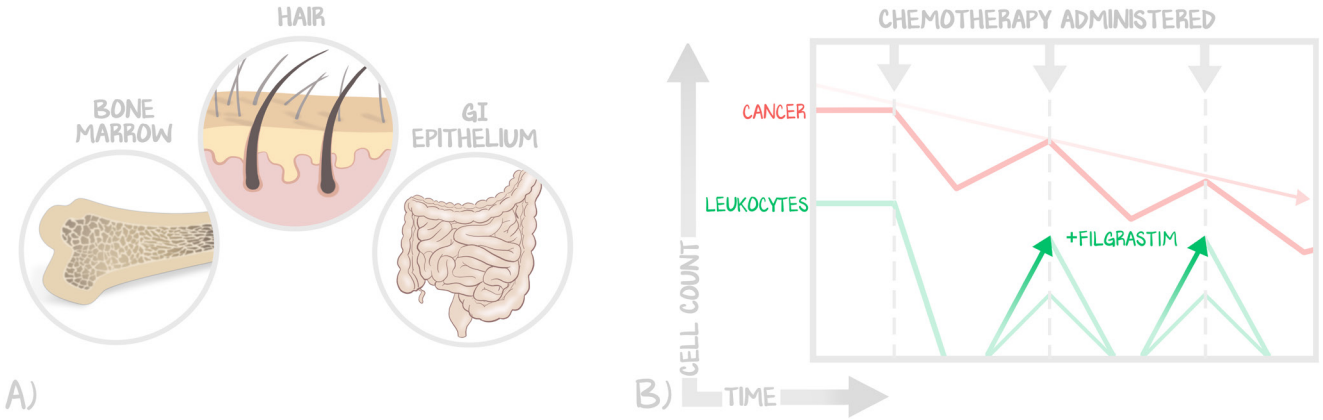

Figure 8.1: Nadir and Affected Cells
(a) The cells most severely impacted by cell-cycle specific chemotherapy are the cells that are mitotically active—GI epithelium, hair follicles, and bone marrow. (b) The number of cells and their response to chemotherapy. We want to kill the cancer cells (top trace) but are limited by how severely we kill good cells, in particular the leukocytes of the bone marrow (bottom trace).

Since many chemotherapeutic agents target the cell cycle, those cells that are mitotically active are vulnerable. **Labile** cells get hit the worst—bone marrow, GI, and hair. This is why the stereotyped chemo patient has **complete hair loss** (hair) and suffers from terrific **nausea**, **vomiting**, and **diarrhea**. What we as providers are most concerned with is their bone marrow. Hair loss is embarrassing and stigmatizing. Nausea sucks. **Neutropenia kills**.

Bone marrow suppression, **gastrointestinal upset**, and **hair loss** are common to almost all chemotherapy agents. It's safer to learn the ones that DON'T cause these than those that do.

Pancytopenia is the **limiting factor** to how aggressively the chemo can be applied. The more damage the chemo does to the bone marrow, the more damage it does to the tumor. So we track the **nadir**—the lowest value the blood counts get after a chemo administration. If the patient hits a count of 0, the chemo was too much, so the next dose will be reduced. If the patient stays above 0, the next dose can be increased. The cancer cells nadir, too. When the chemo wears off, cancer cells and bone marrow start

proliferating again. The game is to give chemo when the patient can tolerate it (the count has recovered), give enough to get as much cancer as possible but not so much that the patient loses marrow, and hope that the proliferation of the marrow outcompetes the proliferation of the cancer.

All cell lines are affected—red blood cells (**anemia**), platelets (**thrombocytopenia**), and white cells (**leukopenia**). If they bleed and have low platelets, they can get **platelet transfusions**. If they have symptomatic anemia, they can get a **blood transfusion**. But **white cells absolutely cannot be transfused**. Unless there were preparation and the recipient of those white cells were the original donor, transfusing someone else's white cells into a patient will cause those transfused white cells to activate an immune response widespread Graft vs Host Disease. In other words, chemo kills white cells; we can't transfuse white cells; no white cells is lethal. What to do?

Nadir Cytokines

We give these colony stimulators in an attempt to give the marrow a boost. If the cancer is of bone marrow, giving this will only stimulate the cancer, so avoid in hematologic malignancies. Each person's cancer is unique, each person's response to chemotherapy consistent for the patient but unpredictable until it's tried. It may be they need a boost to one cell line only. So don't assume that all three must be given.

Cytokine	Goal	
Filgrastim	WBC	Neutropenic fever is defined by Temp > 38° C and < 1,000 PMNs
Erythropoietin	RBC	
Thrombopoietin	Platelets	

Table 8.1: Bone Marrow Cytokines
Link the name of the cytokine to the bone marrow cell it increases.

Cell-Cycle-Specific Drugs

Drugs that act on the phases of the cell cycle are called **cell-cycle specific (CCS).** These drugs are dependent on the mitotic rate of the tumor. Tumors with the highest turnover are the most vulnerable. Indolent, slowly dividing tumors are less susceptible.

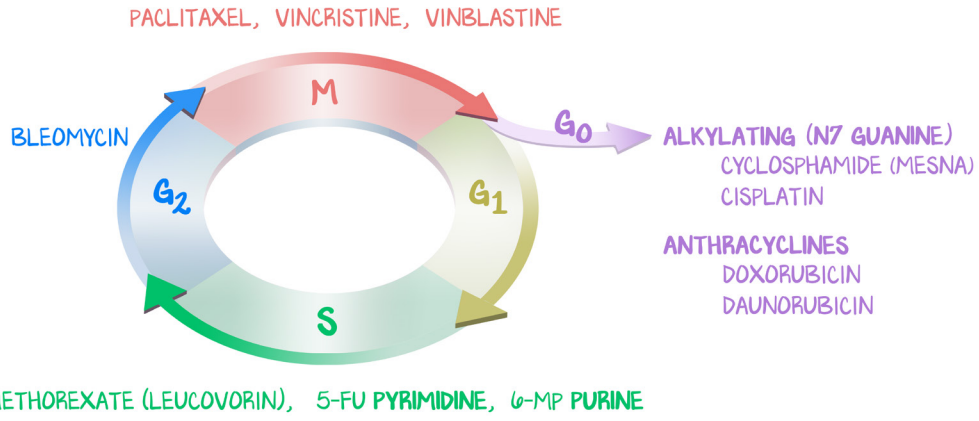

Figure 8.2: Key chemotherapeutics and where they work on the cell cycle
In addition to the side effect profile (Chemo Man, below) memorizing where these key chemotherapeutic agents exact their effect on the cell cycle is the crucial information to know for the preclinical sciences.

S-phase drugs. There are three worth knowing—methotrexate, 5-fluorouracil, and 6-mercaptopurine.

Methotrexate inhibits **Di-Hydro-Folate (DHF) reductase**, inhibiting all DNA synthesis. The side effects to healthy tissue can be mitigated with what is called **leucovorin** rescue. **5-fluorouracil** is a uracil analog (a pyrimidine), but a bad uracil, which **inhibits thymidylate synthetase**, preventing any cell's ability to make thymine. Finally, **6-mercaptopurine** is a purine analog that is used both in autoimmune disorders (interrupting synthesis of rapidly proliferating lymphocytes) and cancer.

G_2 phase has only one to know: **bleomycin** (see Chemo Man). Bleomycin complexes with iron and oxygen, causing DNA strand scission. Bleomycin is known for its **pulmonary side effects**, inducing **pulmonary fibrosis.**

Mitosis-phase drugs target microtubules and spindle formation. They are the vinca alkaloids and paclitaxel.

The vinca alkaloids are the drugs **vincristine** and **vinblastine** (see Chemo Man), which are known to cause **peripheral neuropathy**. They block tubulin heterodimer **polymerization**, meaning that already-built microtubules fall apart and no new microtubules can be built. These drugs **prevent the assembly of the mitotic spindle**. Therefore, on microscopy, no mitotic spindle is seen, and chromatid separation cannot occur.

Another mitosis-phase drug is **paclitaxel**. It also affects the mitotic spindle. But it prevents the **depolymerization**, the disassembly of the tubulin dimers. After cytokinesis, when the spindle is no longer required and the tubulin dimers are harvested to reconstruct cytoskeletal microtubules, the microtubule spindle cannot be taken apart. **Long mitotic spindles persist after cell division.**

Cell-Cycle-Nonspecific Drugs

There are no drugs that are considered G_1 agents. Agents that work in G_1 or G_0 are considered **cell-cycle-nonspecific.** They bind to and damage DNA. Because they do not rely on the cell cycle, they are effective on tumors with low mitotic rates. That also means they can cause side effects (such as anthracycline cardiotoxicity, which induces heart failure) on organs that have permanent cells.

Alkylating agents attack the nitrogen at the 7 position on guanine (**guanine N7**). The two to know are cyclophosphamide and cisplatin. Both are on Chemo Man. **Cyclophosphamide** causes **hemorrhagic cystitis** and bone marrow suppression. Treating with the antidote **mesna** is protective. **Cisplatin** does **not cause bone marrow suppression**, but can cause ototoxicity (hearing) and nephrotoxicity.

Anthracyclines form free radicals and inhibit topoisomerase. The two to know are doxorubicin and daunorubicin, which cause **irreversible** and **dose-dependent systolic heart failure**.

Specialized Targeted Therapies: Monoclonal Antibodies

By targeting something the cancer has but healthy cells don't, the side effects can be reduced and the effectiveness of the therapy improved—in theory. These drugs target tyrosine receptor kinases.

Drug	Target	Cancer and Notes
Imatinib	BCR-ABL	CML
Trastuzumab	HER2/neu	Breast (reversible, non-dose-dependent CHF)
Bevacizumab	VEGF	Colon (angiogenesis)
Sorafenib	VEGF	HCC

Table 8.2: Monoclonal Antibodies
Drugs that target intracellular mechanisms associated with cancer.

Chemo Man

This is an advanced organizer for commonly tested side effects. The lungs are in the shape of a **B** for **Bleomycin**, to help remember pulmonary fibrosis. The arms and legs are in the shape of a **V** for **Vincristine** and **Vinblastine**, which cause peripheral neuropathy. The ears and kidneys are in the shape of a **C** for **Cisplatin**, prompting recall of the ototoxic and nephrotoxic side effects. The heart has two **atria** for the two **anthracyclines** that cause cardiac toxicity (don't forget about the breast cancer drug trastuzumab which also causes CHF). And the bicycle at the bottom of the half-pipe, where the bladder should be, is for remembering that **cyclophosphamide** causes **hemorrhagic cystitis.**

Figure 8.3: Chemo Man
The advanced organizer for how to remember which organs are affected by which chemotherapeutic agents, and to prompt recollection of the side effect they cause.

Danger

Amifostine (cisplatin rescue) and dexrazoxane (doxorubicin rescue) have been removed from the market. They have, however, been erroneously listed as active therapies in review materials for years. They should never be used.